REMARKS

In the Office Action dated September 22, 2004, claims 1-10 and 23-29 were rejected as being non-enabled under 35 USC 112, first paragraph. In support of this rejection, the Examiner provided a five part analysis involving: 1) Nature of the invention; 2) Breadth of the claims; 3) State of the Art; 4) Number of working examples and Guidance provided by Applicant; and 5) Unpredictablility of the art and Amount of Experimentation required.

With respect to the nature of the invention, applicant amends the claims to more particularly point out the nature and asserted utility of the present invention. Specifically, the claims are amended to point out that applicant's claimed composition of matter is to be used for "delivering an eye-specific therapeutic gene to an ocular cell". As set forth in paragraphs 8-12 of the specification, the asserted utility of the present invention is to solve a "delivery" problem with respect to introducing therapeutic genes into ocular cells. The specification states "In most cases, the mutated gene that causes RP is known, and the gene has been cloned. Therefore, gene discovery is no longer the rate-limiting issue in the gene therapy of RP. Rather, the rate-limiting problem is how to target the therapeutic gene throughout the entire retina."(Paragraph 9).

The asserted utility of the present invention is not therapy or diagnosis. Instead, the asserted utility of the present invention involves a solution to the problem outlined above of how to deliver a known therapeutic agent to ocular cells. The present amendment of the claims particulary points out that the utility of the invention is "delivery" to ocular cells. It should also be pointed out that applicant has dropped the term "diagnostic agent" from the claims. Accordingly, the Examiner's various positions with respect to diagnosis as an asserted utility are moot.

Applicant's invention is a receptor-specific liposome that functions as a delivery vehicle for introducing genes into ocular cells. The gene that is encapsulated in the internal compartment of the liposome is only one of four elements that make up the claimed composition. Applicant has chosen to define the type of genes that are encapsulated by identifying the type of agent that the gene expressess. Applicant submits that the use of

"therapeutic agent" to define the gene that is encapulated in the liposome should not be used to imply an asserted utility ot "gene therapy". Instead, the claims, as now amended, and the specification show that the nature of the invention and asserted utility is a composition for use as a new delivery vehicle that is specific for ocular cells.

With regards to the breadth of the claims, applicant disagrees with the Examiner's characterization that the claims encompass a "vast number" of genes. One of ordinary skill in the art is well aware of those genes that express therapeutic agents that are known to be useful useful in treating ocular cells *in vivo*. It is these genes with known therapeutic value that are encompassed by the claims. This is a well-defined group of genes that are either known to those of ordinary skill or can be determined by routine experimentation. In addition, at least 16 different examples of genes that that are known to express exemplary ocular therapeutic agents are listed in the specification (see Paragraph 39).

With regards to the State of the art, Verma is relied on by the Examiner to indicate that the use of "cationic" lipids (ie., liposomes) for gene therapy purposes suffers from an inabiltiy to efficiently deliver and sustain the exprssion therapeutic genes (Page 4, lines 8-10 of Office Action). It is important to point out the the receptor-specific liposomes claimed by applicant are <u>not</u> cationic liposomes. Applicants liposomes include conjugation agents that render the liposome anionic. The following Table sets forth a summary of the differences between the cationic liposomes that Verma discusses and the anionic liposomes of the present invention.

TABLE

Property	Cationic liposomes(Verma)	Applicant's liposomes
DNA packaging	DNA is exterior to polymeric mixture of anionic DNA and cationic lipid	DNA is in interior of 85-100 nm nanocontaine
stable in saline	NO; forms micron sized aggregates in saline	YES
stable in serum	NO; inactivated by serum	YES

TABLE (Continued)

| Property	Cationic liposomes(Verma)	Applicant's liposomes
embolizes in lung after intravenous injection	YES; secondary to aggregation in saline	NO
delivery to eye after intravenous injection	NO; does not cross BRB	YES; crosses BRB
toxic to tissues	YES	NO
net charge of lipid	cationic	anionic

BRB: blood-retinal barrier

The teachings of unpredictability set forth by Verma with respect to cationic liposomes are not relevant to applicants invention that involves a substantially different liposome delivery system, which Verma clearly was not aware of. Applicant's new composition actually solves the problems that Verma was referencing with regards to the use of cationic liposomes.

With regards to the Number of working examples and Guidance provided by applicant, the Examiner's statement that the example showing delivery and expression of ß-galactosidase in ocular cells was *in vitro* is incorrect. A careful review of the examples show that the expression was *in vivo*. As set forth in the Brief Description of the Drawings, FIG. 5C shows "the β-galactosidase histochemistry in an eye obtained 48 hours after <u>intravenous injection</u> of the SV40/β-galactosidase plasmid in accordance with the present invention. There is diffuse expression of the trans-gene in the outer retina, as well as the iris and ciliary body"(emphasis added). This is a clear demonstration of the asserted utility of the claimed composition for delivering a gene to the eye *in vivo* where it is expressed in the outer retina, iris and ciliary body. This expression, which was measured after 48 hours, was not transitory as indicated by the Examiner. With regard to the Examiner's position that the specification lacks examples showing delivery of specific genes expressing an ocular therapeutic agent, the examples showing the delivery and expression of the ß-galactosidase gene <u>in vivo</u> are easily extended by one of ordinary skill in the art to any of the specific genes listed in the

specification and other genes that express an ocular therapeutic agent. The example demostrates the *in vivo* delivery and expression of a gene. This provides a clear solution to the deficiencies of the state of the art, as exemplified by Verma, where unpredictable problems were being experienced when cationic liposomes were used as gene delivery vehicles.

The non-transitory nature of the gene expression provided when genes are delivered in accordance with the present invention has been further supported by tests done on Rhesus monkey retinas by applicant. The results are shown in the Figure below which depicts Luciferase gene expression in the Rhesus monkey retina. Retinal luciferase activity is shown for 3 rhesus monkeys sacrificed at 2, 7, or 14 days after intravenous administration of a luciferase expression plasmid encapsulated in pegylated immunoliposomes (PILs) targeted with a monoclonal antibody (MAb) to the human insulin receptor (HIR) as set forth in the present application. The data were fit to a single-exponential equation to yield the slope/half-time ($t_{1/2}$) and the intercept, [A(0)]. The horizontal line shows the A(0) of luciferase activity in control mouse brain, 0.22 ± 0.08 pg/mg, which indicates the level of gene expression in the monkey retina is still above the therapeutic level for at least 2 weeks after injection. The luciferase expression plasmid was under the influence of the SV40 promoter in these studies. Error bars representing the standard deviation are shown over each closed circle. The time-dependent loss of gene expression in the eye means that gene expression with this system is *reversible*. The reversibility is due to the lack of permanent integration in the host genome, which can lead to insertional mutagenesis, which can cause cancer. The reversibility of gene expression is by design, so as to eliminate the problem of insertional mutagenesis, which is a feature of many viral gene therapy vectors.
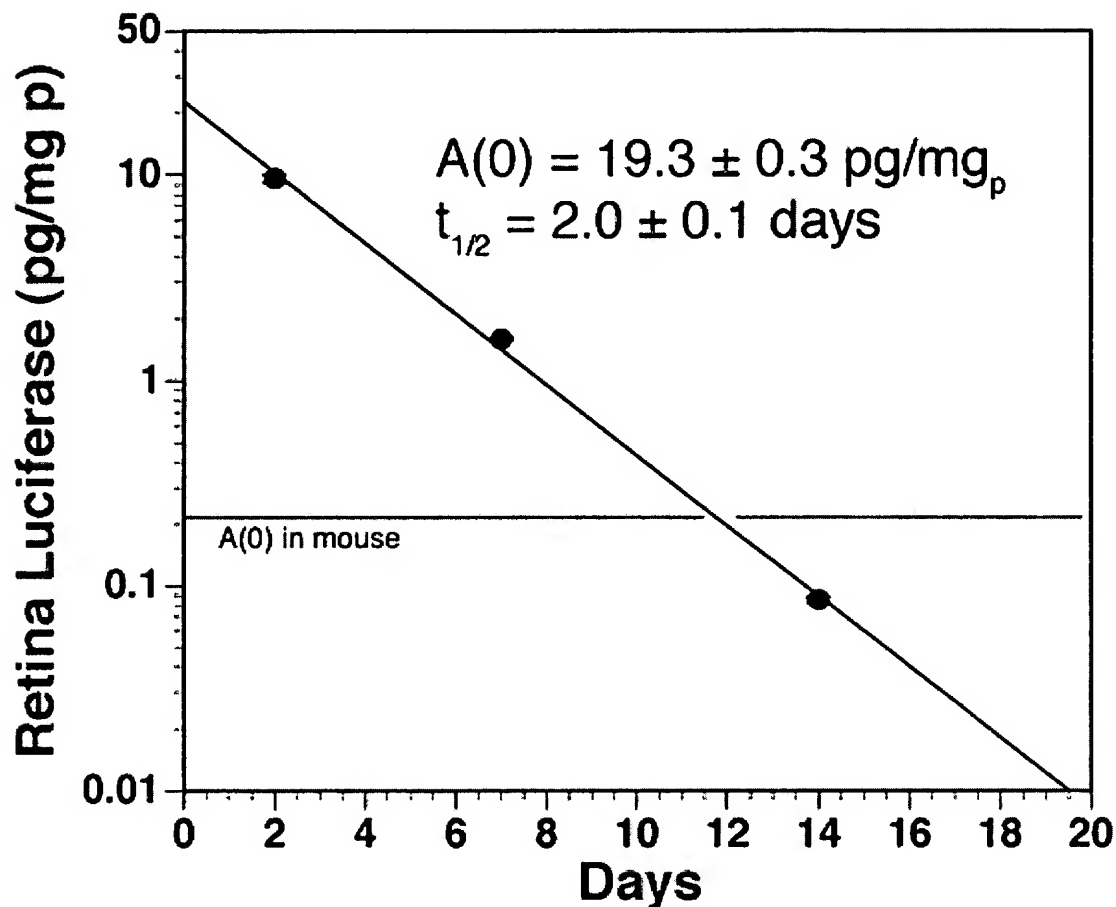
The above additional tests further support the showing in the specification that the receptor-specific liposomes in accordance with the present invention are effective to provide the utility asserted and claimed by applicant, which is delivery and expression of genes *in vivo* to ocular cells.

With regards to Unpredictability of the art and Amount of experimentation required, applicant disagrees with the Examiner's characterization of the claimed invention, and its use, as being "highly unpredictable". The Examiner's basis for this position is based on equating the problems and unpredictability associated with the <u>cationic</u> liposomes described by Verma with applicant's <u>anionic</u> liposomes. As discussed above, applicant's liposomes solve the "delivery" problems associated with cationic liposomes that are the subject of Verma's concerns. Accordingly, there is nothing unprectable about the use of applicant's composition as a gene delivery vehicle nor is undue experimentation required.

One of ordinary skill, in order to use the claimed composition, is initially required to determine if the gene to be encapsulated is known to express a therapeutic agent for the eye. This information is widely available in the literature, on the internet and specific examples are given in the specification. For example, a partial list of ocular diseases and candidate genes for ocular gene therapy are listed in the following table. All of this information is availble using a routine literature or internet search.

Disease	gene
ACQUIRED BLINDNESS:	
Acquired macular degeneration (AMD)	pigment epithelium-derived factor (PEDF)
Diabetic retinopathy (DR)	RNA interference (RNAi) based gene therapy to knock down vascular endothelial growth factor (VEGF)
INHERITED BLINDNESS:	
Leber congenital amaurosis (LCA)	RPE65
Retinitis pigmentosa (RP)	rhodopsin (RHO)
	Phosphodiesterase (PDE)-α or -β
	Peripherin (RDS)
	Rod outer segment protein-1 gene (ROM1)
Stargardt disease	rim protein gene (ABC-R)
Multiple diseases of the eye	>50 gene mutations listed at Retnet**

**Retnet retinal network listing of Cloned and/or Mapped Genes Causing Retinal Diseases and blindness:

http://www.sph.uth.tmc.edu/Retnet/disease.htm

Once the appropriate gene has been selected, it is combined with the liposome, targeting agent and conjugation agent as described in the specification to form the claimed composition. This composition is then used to "deliver" the gene to ocular cells where it is expressed. There is no undue or difficult amount of experimentation required to use the

invention to achieve the asserted utility of delivery and expression. It is beyond the scope of applicants invention to predict and provide enablement regarding whether the resulting gene expression will actually provide a cure (sucessful therapy) for a disease or possibly cause undesirable side effects. Instead, applicants invention, and the asserted utility, is directed towards a new liposome-based gene delivery system that, in contrast to the out dated teachings of Verma, actually does deliver and express a gene in ocular cells.

Applicant respectfully requests that this application be reexamined in view of the above amendments and remarks and that the claims, as now amended, be allowed.

Respectfully Submitted,

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